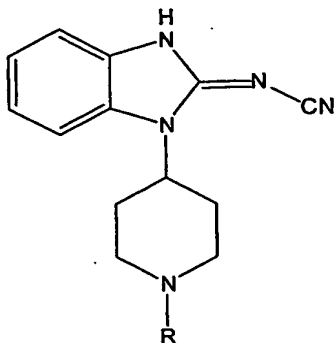


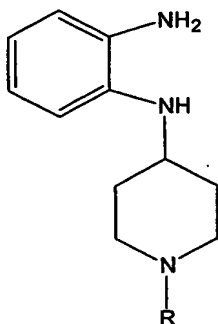
We claim:

1. A process for synthesizing a compound of formula (V):



(V)

comprising reacting a compound of formula (IV):



(IV)

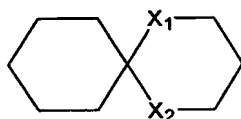
with (A)(A₁)-cyanocarbonimidate to form a compound of formula (V);
 wherein A and A₁ are independently selected from methyl, ethyl propyl,
 phenyl and benzyl; and wherein,

R is Z-R₁, wherein

Z is selected from the group consisting of a bond, straight or branched C₁₋₆
 alkylene, -NH-, -CH₂O-, -CH₂NH-, -CH₂N(CH₃)-, -NHCH₂-, -CH₂CONH-, -
 NHCH₂CO-, -CH₂CO-, -COCH₂-, -CH₂COCH₂-, -CH(CH₃)-, -CH=, -O- and -

HC=CH-, wherein the carbon and/or nitrogen atoms are unsubstituted or substituted with one or more lower alkyl, hydroxy, halo or alkoxy group;

R₁ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₃₋₁₂cycloalkyl, C₂₋₁₀alkenyl, amino, C₁₋₁₀alkylamino-, C₃₋₁₂cycloalkylamino-, -COOV₁, -C₁₋₄COOV₁, cyano, cyanoC₁₋₁₀alkyl-, cyanoC₃₋₁₀cycloalkyl-, NH₂SO₂-, NH₂SO₂C₁₋₄alkyl-, NH₂SOC₁₋₄alkyl-, aminocarbonyl-, C₁₋₄alkylaminocarbonyl-, diC₁₋₄alkylaminocarbonyl-, benzyl, C₃₋₁₂ cycloalkenyl-, a monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, a hetero-monocyclic ring, a hetero-bicyclic ring system, and a spiro ring system of the formula (XI):



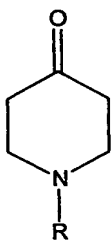
(XI)

wherein X₁ and X₂ are independently selected from the group consisting of NH, O, S and CH₂; and wherein said alkyl, cycloalkyl, alkenyl, C₁₋₁₀alkylamino-, C₃₋₁₂cycloalkylamino-, or benzyl of R₁ is optionally substituted with 1-3 substituents selected from the group consisting of halogen, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, nitro, trifluoromethyl-, cyano, -COOV₁, -C₁₋₄COOV₁, cyanoC₁₋₁₀alkyl-, -C₁₋₅(=O)W₁, -C₁₋₅NHS(=O)₂W₁, -C₁₋₅NHS(=O)W₁, a 5-membered heteroaromaticC₀₋₄alkyl-, phenyl, benzyl, benzyloxy, said phenyl, benzyl, and benzyloxy optionally being substituted with 1-3 substituents selected from the group consisting of halogen, C₁₋₁₀ alkyl-, C₁₋₁₀ alkoxy-, and cyano; and wherein said C₃₋₁₂ cycloalkyl, C₃₋₁₂ cycloalkenyl, monocyclic, bicyclic or tricyclic aryl, heteroaryl ring, hetero-monocyclic ring, hetero-bicyclic ring system, or spiro ring system of the formula (XI) is optionally substituted with 1-3 substituents selected from the group consisting of halogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, nitro, trifluoromethyl-, phenyl, benzyl, phenoxy and benzyloxy, wherein said phenyl, benzyl, phenoxy or benzyloxy is optionally substituted with 1-3 substituents selected from the group consisting of halogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, and cyano;

wherein V₁ is independently selected from H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, benzyl and phenyl; and

wherein W_1 is hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl, C_{1-10} alkoxy, C_{3-12} cycloalkoxy, $-CH_2OH$, amino, C_{1-4} alkylamino-, or diC_{1-4} alkylamino-.

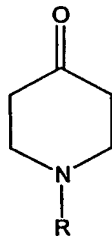
2. The process of claim 1, wherein the compound of formula (IV) is formed by subjecting a compound of formula (III):



(III)

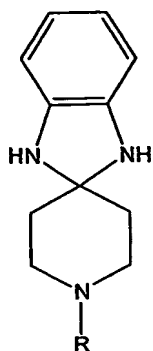
to reductive amination with 1,2-phenylenediamine, an acid and a reducing agent to form a compound of formula (IV).

3. The process of claim 1, wherein the compound of formula (IV) is formed by subjecting a compound of formula (III):



(III)

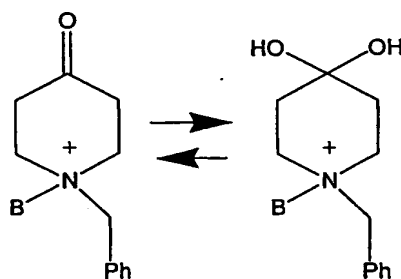
to amination with 1,2-phenylenediamine and an acid to form a compound of formula (IIIA):



(IIIA)

and reducing the compound of (IIIA) with a reducing agent to form a compound of formula (IV).

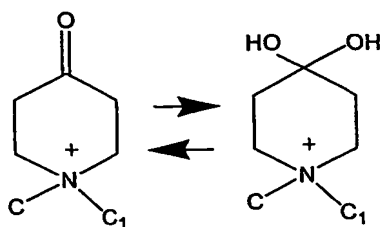
4. The process of claim 2 or 3, wherein the compound of formula (III) is formed by reacting a compound of formula (II):



(II)

with R-amine to form a compound of formula (III);
wherein B is selected from the group consisting of methyl, ethyl and propyl.

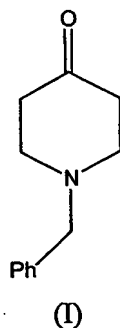
5. The process of claim 2 or 3, wherein the compound of formula (III) is formed by reacting a compound of formula (IIA):



(IIA)

with R-amine to form a compound of formula III;
 wherein C and C₁ are independently selected from the group consisting of
 methyl,
 ethyl and propyl.

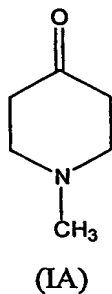
6. The process of claim 4, wherein the compound of formula (II) is formed by
 reacting a compound of formula (I):



(I)

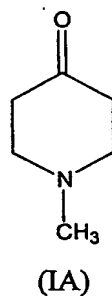
with an C₁₋₃alkyl-halogen to form a compound of formula (II).

7. The process of claim 4, wherein the compound of formula (II) is formed by
 reacting a compound of formula (IA):



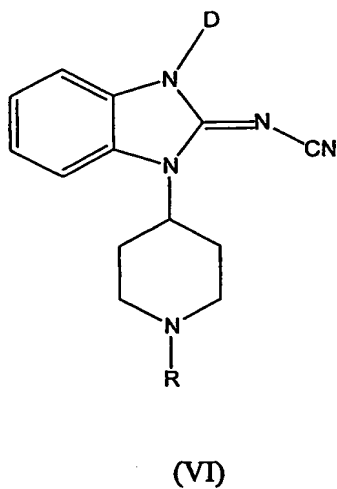
with a benzyl-halogen to form a compound of formula II.

8. The process of claim 4, wherein the compound of formula (IIA) is formed by reacting a compound of formula (IA):



with (C)(C₁)sulphate to form a compound of formula (IIA).

9. The process of claim 1, further comprising reacting a compound of formula (V) with a D-halogen to form a compound of formula (VI):



wherein D is selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl,

C₃₋₁₂ cycloalkylC₁₋₄alkyl-, C₁₋₁₀ alkoxy, C₃₋₁₂ cycloalkoxy-, C₁₋₁₀ alkyl substituted with 1-3 halogen, C₃₋₁₂ cycloalkyl substituted with 1-3 halogen, C₃₋₁₂ cycloalkylC₁₋₄alkyl- substituted with 1-3 halogen, C₁₋₁₀ alkoxy substituted with 1-3 halogen, C₃₋₁₂ cycloalkoxy- substituted with 1-3 halogen, -COOV₁, -C₁₋₄COOV₁, -CH₂OH, -SO₂N(V₁)₂, hydroxyC₁₋₁₀alkyl-, hydroxyC₃₋₁₀cycloalkyl-, cyanoC₁₋₁₀alkyl-, cyanoC₃₋₁₀cycloalkyl-, -CON(V₁)₂, NH₂SO₂C₁₋₄alkyl-, NH₂SOC₁₋₄alkyl-, sulfonylaminoC₁₋₁₀alkyl-, diaminoalkyl-, -sulfonylC₁₋₄alkyl, a 6-membered heterocyclic ring, a 6-membered heteroaromatic ring, a 6-membered heterocyclicC₁₋₄alkyl-, a 6-membered heteroaromaticC₁₋₄alkyl-, a 6-membered aromatic ring, a 6-membered aromaticC₁₋₄alkyl-, a 5-membered heterocyclic ring optionally substituted with an oxo or thio, a 5-membered heteroaromatic ring, a 5-membered heterocyclicC₁₋₄alkyl- optionally substituted with an oxo or thio, a 5-membered heteroaromaticC₁₋₄alkyl-, -C₁₋₅(=O)W₁, -C₁₋₅(=NH)W₁, -C₁₋₅NHC(=O)W₁, -C₁₋₅NHS(=O)₂W₁, -C₁₋₅NHS(=O)W₁, and a 5-membered heteroaromatic ring optionally substituted with 1-3 lower alkyl

wherein V₁ is independently selected from H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, benzyl and phenyl; and

wherein W₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₁₀ alkoxy, C₃₋₁₂ cycloalkoxy, -CH₂OH, amino, C₁₋₄alkylamino-, or diC₁₋₄alkylamino-; and

wherein each V₁ and W₁ is the same or different.

10. The process of claim 1, wherein R₁ is selected from the group consisting of C₁₋₁₀ alkyl and C₃₋₁₂cycloalkyl.

11. The process of claim 1, wherein R is cyclooctyl.

12. The process of claim 1, wherein A and A₁ are both phenyl.

13. The process of claim 1, wherein the reaction is performed in a solvent.

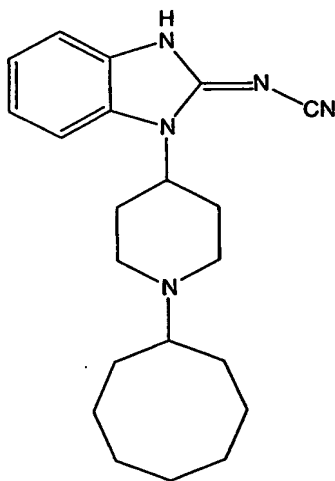
14. The process of claim 13, wherein the solvent is selected from acetonitrile, dimethylformamide, or a mixture thereof.

15. The process of claim 1, wherein the reaction is performed at a temperature of about 50° C to about 125° C or about 75° C to about 125 ° C or about 100 ° C.
16. The process of claim 15, wherein a portion of the reaction is performed under ambient temperature.
17. The process of claim 1, comprising isolating an intermediate cyanoimide.
18. The process of claim 17, comprising preparing the compound of formula (V) in a one pot reaction in acetonitrile, dimethylformamide, or a mixture thereof.
19. The process of claim 2, wherein the reductive amination is performed in a suitable solvent.
20. The process of claim 19, wherein the solvent is dichloroethane, tetrahydrofuran or a mixture thereof.
21. The process of claim 2, wherein the acid is acetic acid, propionic acid, paratoluenesulfonic acid, or a mixture thereof.
22. The process of claim 22, wherein the reducing agent is selected from the group consisting of sodium triacetoxyborohydride, sodium acetoxyborohydride, sodium borohydride, lithium borohydride, lithium aluminum hydride and a combination thereof.
23. The process of claim 23, wherein the reducing agent is lithium aluminum hydride.
24. The process of claim 2, wherein the reductive amination is performed at ambient temperature.
25. The process of claim 3, wherein the amination is performed in a solvent.

26. The process of claim 25, wherein the solvent is dichloroethane, tetrahydrofuran or a mixture thereof.
27. The process of claim 3, wherein the acid is acetic acid, propionic acid, paratoluenesulfonic acid, or a mixture thereof.
28. The process of claim 3, wherein the compound of formula (IIIA) is recovered.
29. The process of claim 28, wherein the compound of formula (IIIA) is recovered as a gum.
30. The process of claim 28, wherein the recovered compound of formula (IIIA) is dissolved in a solvent and reduced with the reducing agent.
31. The process of claim 30, wherein the reducing agent is selected from the group consisting of sodium triacetoxyborohydride, sodium acetoxyborohydride, sodium borohydride, lithium borohydride, lithium aluminum hydride and a combination thereof.
32. The process of claim 31, wherein the reducing agent is lithium aluminum hydride.
33. The process of claim 3, wherein the reduction is initiated at a temperature below about 10° C and raised to a temperature of about 30° C to about 70° C.
34. The process of claim 4 or 5, wherein the reaction to form compound (III) is performed in a solvent.
35. The process of claim 34, wherein the solvent is an alcohol, water or a mixture thereof.
36. The process of claim 35, wherein the solvent is ethanol and water.

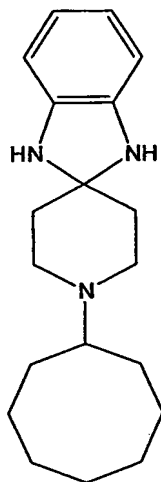
37. The process of claim 34, wherein the reaction is performed under reflux conditions.
38. The process of claim 6, wherein the C₁₋₃alkyl-halogen is iodomethane.
39. The process of claim 6, wherein the reaction is performed in a solvent.
40. The process of claim 39, wherein the solvent is selected from acetone, ethyl acetate, toluene, hexane, cyclohexane, and mixtures thereof.
41. The process of claim 39, wherein the reaction is performed under reflux conditions.
42. The process of claim 7, wherein the halogen is bromide.
43. The process of claim 7, wherein the reaction is performed in a solvent.
44. The process of claim 43, wherein the solvent is selected from acetone, ethyl acetate, toluene, hexane, cyclohexane, and mixtures thereof.
45. The process of claim 43, wherein the reaction is performed under reflux conditions.
46. The process of claim 8, wherein C and C₁ are both methyl.
47. The process of claim 8, wherein the reaction is performed in a solvent.
48. The process of claim 47, wherein the solvent is selected from acetone, ethyl acetate, toluene, hexane, cyclohexane, and mixtures thereof.
49. The process of claim 47, wherein the compound of formula (IA) and the solvent are cooled to a temperature below 10° C prior to the addition of the (C)(C₁)sulphate.

50. The process of claim 9, wherein D in D-halogen is $-\text{CH}_2\text{CONH}_2$.
51. The process of claim 9, wherein the halogen in D-halogen is bromide.
52. The process of claim 9, wherein the reaction is performed in a solvent.
53. The process of claim 52, wherein the solvent is tetrahydrofuran, dimethylformamide, or a mixture thereof.
54. The process of claim 52, wherein the reaction is initiated at ambient temperature and raised to a temperature of about 50°C or less.
55. The process of claim 1, further comprising converting the compound of formula (V) to a pharmaceutically acceptable acid-addition salt.
56. The process of claim 9, further comprising converting the compound of formula (VI) to a pharmaceutically acceptable acid-addition salt.
57. The compound:



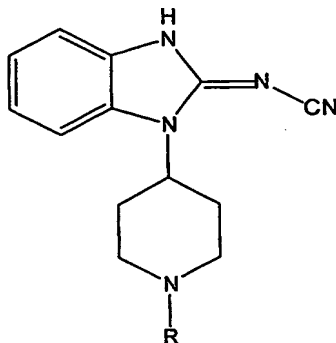
or a salt thereof.

58. A pharmaceutical composition comprising a compound of claim 57 and a pharmaceutically acceptable carrier thereof.
59. A method of treating pain comprising administering to a patient in need thereof, an effective amount of a compound of claim 57.
60. A method of modulating a pharmacological response from the ORL1 receptor comprising administering to a patient in need thereof an effective amount of a compound according to claim 57 to agonize the ORL1 receptor.
61. The compound:



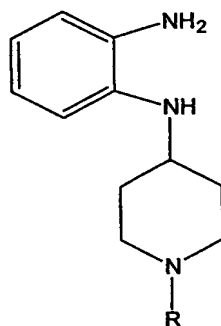
62. The process of claim 2, wherein R is cyclooctyl.
63. The process of claim 3, wherein R is cyclooctyl.
64. The process of claim 4, wherein R in R-amine is cyclooctyl.
65. The process of claim 5, wherein R in R-amine is cyclooctyl.
66. The process of claim 9, wherein Z is a bond and R₁ is cyclooctyl.

67. A process for synthesizing a compound of formula (V):



(V)

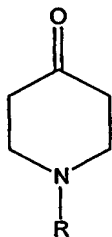
comprising reacting a compound of formula (IV):



(IV)

with (A)(A₁)-cyanocarbonimidate to form a compound of formula (V);
wherein A and A₁ are independently selected from methyl, ethyl, propyl,
phenyl and benzyl; and wherein,
R is cyclooctyl

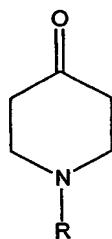
68. The process of claim 1, wherein the compound of formula (IV) is formed by
subjecting a compound of formula (III):



(III)

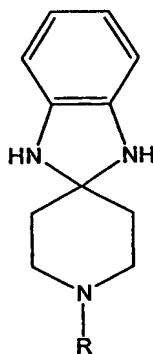
to reductive amination with 1,2-phenylenediamine, an acid and a reducing agent to form a compound of formula (IV).

69. The process of claim 1, wherein the compound of formula (IV) is formed by
subjecting a compound of formula (III):



(III)

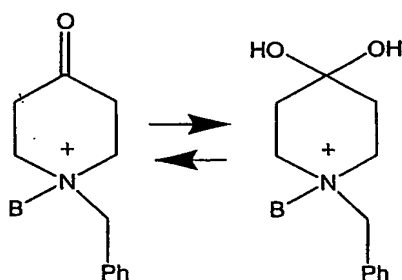
to amination with 1,2-phenylenediamine and an acid to form a compound of formula (IIIA):



(IIIA)

and reducing the compound of (IIIA) with a reducing agent to form a compound of formula (IV).

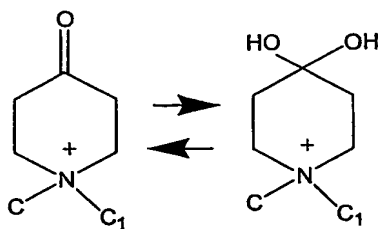
70. The process of claim 2 or 3, wherein the compound of formula (III) is formed by reacting a compound of formula (II):



(II)

with R-amine to form a compound of formula (III);
wherein B is selected from the group consisting of methyl, ethyl and propyl.

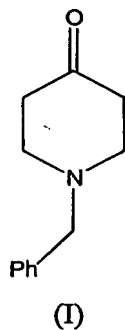
71. The process of claim 2 or 3, wherein the compound of formula (III) is formed by reacting a compound of formula (IIA):



(IIA)

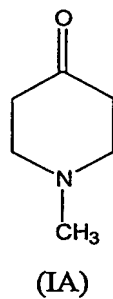
with R-amine to form a compound of formula III;
wherein C and C₁ are independently selected from the group consisting of methyl, ethyl and propyl.

72. The process of claim 4, wherein the compound of formula (II) is formed by reacting a compound of formula (I):



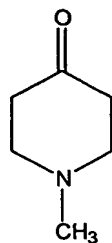
with an C₁₋₃alkyl-halogen to form a compound of formula (II).

73. The process of claim 4, wherein the compound of formula (II) is formed by reacting a compound of formula (IA):



with a benzyl-halogen to form a compound of formula II.

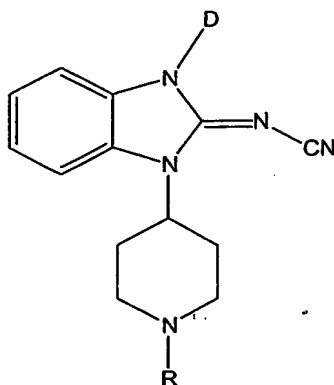
74. The process of claim 4, wherein the compound of formula (IIA) is formed by reacting a compound of formula (IA):



(IA)

with (C)(C₁)sulphate to form a compound of formula (IIA).

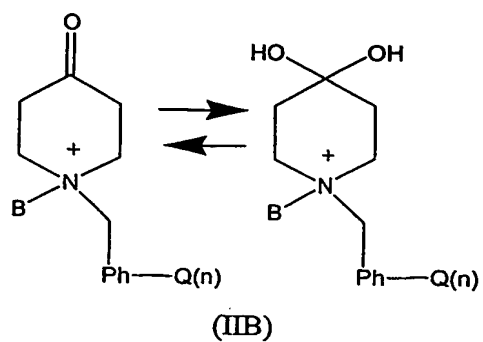
75. The process of claim 1, further comprising reacting a compound of formula (V) with a D-halogen to form a compound of formula (VI):



(VI)

wherein D is CH₂CONH₂.

76. The process of claim 2 or 3, wherein the compound of formula (III) is formed by reacting a compound of formula (IIB):



with R-amine to form a compound of formula (III);

wherein B is selected from the group consisting of methyl, ethyl and propyl; Q is a member selected from the group consisting of COOH, or an ester group; and n an integer from 1-3.